אפריל 2022

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת רז רוקחות מבקשת להודיעכם על עדכון העלון לרופא של התכשיר:

METOCLOPRAMIDE S.A.L.F 10 MG/2 ML

בהודעה זו מצוינים רק הסעיפים בהם נעשו שינויים מהותיים בעלון לרופא.

התוספות סומנו בצבע כחול , החמרות מודגשות בצהוב והמחיקות סומנו בצבע אדום עם קו מחיקה.

העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות:

www.health.gov.il וניתן לקבלו מודפס על ידי פנייה לבעל הרישום: רז רוקחות בע"מ, רחוב המתכת 6, א.ת. קדימה.

בברכה,

אריאל מימון

רוקחת ממונה

מרכיב פעיל וחוזק:

METOCLOPRAMIDE (AS HYDROCHLORIDE MONOHYDRATE) 10 MG / 2 ML

התוויה מאושרת:

METOCLOPRAMIDE S.A.L.F 10 MG/2 ML is indicated in adults for:
- Prevention of postoperative nausea and vomiting (PONV)
- Prevention of delayed nausea and vomiting caused by chemotherapy (delayed CINV)
- Prevention of nausea and vomiting caused by radiation therapy
- Symptomatic treatment of nausea and vomiting, including nausea and vomiting caused by migraine attack. In migraine attacks, metoclopramide can be used concomitantly with oral analgesics to improve their absorption.
- Diabetic gastroparesis
- To faciliate diagnostic procedures (ie, to faciliate small bowel intubation and as an aid in radiological examinations) Pediatric population.

METOCLOPRAMIDE S.A.L.F 10 MG/2 ML is indicated in children aged 1 to 18 years for:
- Second line-therapy:
Treatment of established postoperative nausea and vomiting (PONV)
- Second-line therapy:
Prevention of delayed nausea and vomiting caused by chemotherapy (delayed CINV)
- To facilitate diagnostic procedures (ie, to faciliate small bowel intubation and as an aid in radiological examinations).

להלן העדכונים המהותיים שבוצעו בעלון לרופא:

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4.2 Posology and method of administration

Posology

Adult patients

For all adult indications except diabetic gastroparesis and facilitation of diagnostic procedures ~~and prevention of PONV~~ (see below):

- The recommended dose is 10 mg, 1 to 3 times a day.
- The maximum recommended daily dose is 30 mg or 0.5 mg/kg bodyweight whichever is lower.
- The maximum recommended treatment period is usually 5 days.

~~For prevention of PONV a single dose of 10mg is recommended.~~

Pediatric patients

For all pediatric indications except facilitation of diagnostic procedures (see below):

- The recommended dose is 0.1 mg to 0.15 mg/kg bodyweight, 1 to 3 times a day.
- The maximum recommended daily dose is 0.5 mg/kg bodyweight.
- The maximum recommended treatment period is usually 5 days ~~for prevention of delayed CINV and 48 hours for treatment of established PONV~~.

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4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Gastrointestinal hemorrhage, mechanical obstruction or gastro-intestinal perforation for which the stimulation of gastrointestinal motility constitutes a risk.
- Confirmed or suspected pheochromocytoma, due to the risk of severe hypertension episodes.
- History of neuroleptic or metoclopramide-induced tardive dyskinesia.
- Epilepsy (increased frequency and intensity ~~of seizures~~).
- Parkinson's disease.
- Combination with levodopa or dopaminergic agonists (see section 4.5)
- Known history of methemoglobinemia with metoclopramide, or of NADH cytochrome- b5 reductase deficiency.
- Use in children less than 1 year of age due to an increased risk of extrapyramidal disorders (see section 4.4).
- Metoclopramide should not be used during the first three to four days following operations such as pyloroplasty or gut anastomosis as vigorous muscular contractions may adversely affect healing.
- Breast-feeding (see Section 4.6).

4.4 Special warnings and precautions for use

If vomiting persists the patient should be reassessed to exclude the possibility of an underlying disorder e.g. cerebral irritation.

Neurological Disorders

Extrapyramidal disorders may occur, particularly in children and young adults, and/or when high doses are used. These reactions usually occur at the beginning of the treatment, and can occur after a single administration. Metoclopramide should be discontinued immediately in the event of extrapyramidal symptoms. ~~When metoclopramide is given intravenously, extrapyramidal disorders are less likely at slower infusion rates. Metoclopramide should be discontinued immediately in the event of extrapyramidal symptoms.~~ These effects are generally completely reversible after treatment discontinuation , but may require a symptomatic treatment (benzodiazepines in children, and/or anticholinergic anti-Parkinsonian medicinal products in adults).

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Cardiac disorders

There have been reports of serious cardiovascular undesirable effects and abnormalities of cardiac conduction including cases of circulatory collapse, severe bradycardia, cardiac arrest and QT prolongation following administration of metoclopramide by injection, particularly via the intravenous route (see section 4.8).

Special care should be taken when administering metoclopramide, particularly via the intravenous route to the elderly population, to patients with cardiac conduction disturbances (including QT prolongation), patients with uncorrected electrolyte imbalance, bradycardia and those taking other drugs ~~medicines~~ known to prolong QT interval.

Special care should be taken when administering metoclopramide intravenously to patients with 'sick sinus syndrome'.

Metoclopramide should be used with care with other drugs affecting cardiac conduction.

Metoclopramide should be used with caution in patients with hypertension, since there is limited evidence that the drug may increase circulating catecholamines in such patients.

Intravenous doses should be administered as a slow bolus (at least over 3 minutes) in order to reduce the risk of adverse effects (e.g. hypotension, akathisia).

Renal and hepatic impairment

In patients with renal impairment or with severe hepatic impairment, a dose reduction is recommended (see section 4.2).

Other precautions :

Metoclopramide may cause elevation of serum prolactin levels.

Care should be exercised when using metoclopramide in patients with a history of atopy (including asthma) or porphyria.

Because metoclopramide can stimulate gastro-intestinal mobility, the drug theoretically could produce increased pressure on the suture lines following gastro-intestinal anastomosis or closure (see section 4.3).

Excipients with known effect:

The drug product contains sodium metabisulphite, which may rarely cause severe hypersensitivity reactions and bronchospasm.

1 ampoule of Metoclopramide S.A.L.F. 10 mg/2 ml contains sodium chloride as isotonicizing agent; the total quantity of sodium is less than 1 mmol (23 mg), i.e. it is essentially sodium-free.

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4.5 Interaction with other medicinal products and other forms of interaction

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Central stimulants

The effects of certain other drugs with potential central stimulant effects, e.g. monoamine oxidase inhibitors and sympathomimetics, may be modified when prescribed with metoclopramide and their dosage may need to be adjusted accordingly.

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4.7 Effects on ability to drive and use machines

Metoclopramide has moderate influence on the ability to drive and use machines.

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4.8 Undesirable effects

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 , <1 /10); uncommon (≥1/1000 , <1/100); rare(≥ 1/10,000 , <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders		
	Not known	Methemoglobinemia, which could be related to NADH cytochrome-b5 reductase deficiency, particularly in neonates in whom the use is contraindicated (see section 4.4). Sulfhemoglobinemia, mainly with concomitant administration of high doses of sulfur-releasing medicinal products
Cardiac disorders		
	Uncommon	Bradycardia~~, particularly with intravenous route~~
	Not known	Cardiac arrest, occurring shortly after injectable use, and which can be subsequent to bradycardia (see section 4.4); Atrioventricular block, Sinus arrest ~~particularly with intravenous route~~; Electrocardiogram QT prolonged; Torsades de pointes
Endocrine disorders*		
	Uncommon	Amenorrhea, Hyperprolactinemia
	Rare	Galactorrhea
	Not known	Gynecomastia
Gastrointestinal disorders		
	Common	Diarrhea
General disorders and administration site conditions		
	Common	Asthenia
	Not Known	Injection site inflammation and local phlebitis
Immune system disorders		
	Uncommon	Hypersensitivity
	Not known	Anaphylactic reaction (including anaphylactic shock) ~~particularly with intravenous route~~
Nervous system disorders		
	Very common	Somnolence
	Common	Extrapyramidal disorders (particularly in children and young adults and/or when the recommended dose is exceeded, even following administration of a single dose of the drug ~~medicine~~) (see section 4.4), Parkinsonism, Akathisia
	Uncommon	Dystonia (including visual disturbances and oculogyric crisis), Dyskinesia, Depressed level of consciousness
	Rare	Convulsion especially in epileptic patients
	Not known	Tardive dyskinesia which may be persistent, during or after prolonged treatment, particularly in elderly patients (see section 4.4), Neuroleptic malignant syndrome (see section 4.4)
Psychiatric disorders		
	Common	Depression
	Uncommon	Hallucination
	Rare	Confusional state
Vascular disorders		
	Common	Hypotension~~, particularly with intravenous route~~
	Not known	Shock, syncope after injectable use. Acute hypertension in patients with pheochromocytoma (see section 4.3) Transient increase in blood pressure
Skin disorders		
	Not known	Skin reactions such as rash, pruritus, angioedema and urticaria

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Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
~~http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il~~

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Agents stimulating gastro-intestinal motility
~~Intestinal motility stimulant~~ ATC code: A03FA01 (Propulsives ~~A: digestive tracts and metabolism~~)
~~Metoclopramide is a neuroleptic dopamine antagonist. It prevents vomiting by blocking dopaminergic sites.~~
Mechanism of action
The action of metoclopramide is closely associated with parasympathetic nervous control of the upper gastro-intestinal tract, where it has the effect of encouraging normal peristaltic action. This provides for a fundamental approach to the control of those conditions where disturbed gastro-intestinal motility is a common underlying factor.
Metoclopramide stimulates activity of the upper gastro-intestinal tract and restores normal co-ordination and tone. Gastric emptying is accelerated and the resting tone of the gastrooesophageal sphincter is increased. Metoclopramide is a dopamine-receptor antagonist with a direct anti-emetic effect on the medullary chemoreceptor trigger zone.

5.2 Pharmacokinetic properties
Absorption
Metoclopramide is rapidly absorbed from ~~in~~ the gastrointestinal ~~digestive~~ tract and undergoes variable first-pass metabolism in the liver.
~~Bioavailability is generally 80%, however it varies between individuals as a result of the liver first pass metabolism effect.~~
~~Distribution~~
~~Metoclopramide is widely distributed in the tissues. The distribution volume is 2.2 to 3.4 L/kg. It does not bind extensively to plasma proteins. It passes through the placenta and into the milk.~~
Biotransformation and Elimination
Metoclopramide is metabolised in the liver and the predominant route of elimination of metoclopramide and its metabolites is via the kidney. It crosses the placenta and is excreted in breast milk. The elimination half-life is about 6 hours. ~~Metoclopramide is not extensively metabolized.~~
~~Elimination~~
~~Metoclopramide is principally eliminated in the urine in free or sulfate conjugated form.~~
~~The elimination half-life is from 5 to 6 hours. It increases in cases of renal or hepatic impairment.~~
Renal impairment
Metoclopramide clearance is reduced by up to 70% in patients ~~suffering from~~ with severe renal impairment, while the plasma elimination half life is increased (approximately ~~about~~ 10 hours for a creatinine clearance of 10-50 mL/minute and 15 hours for creatinine clearance <10 mL/minute).
Hepatic impairment
In patients with cirrhosis of the liver, accumulation of metoclopramide has been observed, associated with a 50% reduction in plasma clearance. ~~Accumulation of metoclopramide was observed in patients suffering from cirrhosis of the liver, accompanied by a 50% decrease in plasma clearance.~~

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6.2 Incompatibilities
~~Injection:~~ Compatibility studies with METOCLOPRAMIDE S.A.L.F 10mg/2ml Injection have not been performed. According to the literature, metoclopramide injection is compatible for dilution with 5% Dextrose, normal saline, Ringer's injection, and Lactated Ringer's injection.